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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/992,680	11/19/2001	Chi-Huey Wong	84503	1046
24628	7590	11/21/2005	EXAMINER	
WELSH & KATZ, LTD 120 S RIVERSIDE PLAZA 22ND FLOOR CHICAGO, IL 60606			PRATS, FRANCISCO CHANDLER	
			ART UNIT	PAPER NUMBER
			1651	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/992,680

Applicant(s)

WONG ET AL.

Examiner

Francisco C. Prats

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 September 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21-26, 28, 29 and 52-57 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21-26, 28, 29 and 52-57 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>9-6-05</u> | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

The amendment filed September 6, 2005, has been received and entered. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claims 21-26, 28, 29 and 52-57 are pending and are examined on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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Claims 21-23, 25, 52, 54 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bergh et al (U.S. Pat. 4,925,796) in view of Prieels et al (J. Biol. Chem. 256(20):10456-10463 (1981)) and Schachter et al (Methods Enzymol. 28:285-287 (1972)).

Bergh discloses compositions comprising a fucosyltransferase and GDP-fucose, for use in fucosylation of oligosaccharide moieties of glycoproteins. See column 18, lines 33-68; see also claim 25 at column 26. Bergh explicitly discloses that suitable fucosyltransferases are those disclosed by Prieels. See column 18, 55-58. Bergh differs from the cited claims in failing to include the claimed GDP-fucose forming enzymes, fucose kinase and GDP-pyrophosphorylase, in his composition. However, Schachter clearly discloses that the GDP-fucose required in the fucosylation process of Bergh can be prepared using the very enzymes recited in the claims. Note the presence of both GDP and GTP in the reaction milieu of Schachter, as evidenced by the reaction equilibrium equation on page 285.

Thus, solely looking to the cited prior art, the artisan of ordinary skill would have been motivated to have combined the enzymes and substrates of Schachter with the fucosyltransferase of Bergh so as to generate the GDP-fucose required for Bergh's

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fucosylation process. Particular motivation for combining the fucosyltransferase of Prieels, as suggested by Bergh, with the GDP-fucose-synthesizing enzymes of Schachter, would have been derived from the disclosure by Prieels that the fucosyltransferases disclosed therein have a fairly wide pH optimum ranging from pH 6.5 to pH 8.5 (Prieels, e.g., Fig. 7, at page 10461), which encompasses the very pH used by Schachter, pH 8 (Schachter, page 285), to prepare GDP-fucose. Thus, the artisan of ordinary skill, recognizing that Bergh's oligosaccharide-synthesizing process requires GDP-fucose as a starting material, and further recognizing from Schachter that the GDP-fucose starting material can be made enzymatically at a pH directly compatible with Bergh's fucosyltransferases (as evidenced by Prieels), clearly would have been motivated to have combined the enzymes responsible for production of the GDP-fucose starting material with the enzyme responsible for producing the oligosaccharide, with a reasonable expectation that the resulting combination of enzymes would result in the production of the oligosaccharide compounds disclosed by Bergh as being desirable. A holding of obviousness is therefore required.

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Claims 21-25, 52, and 54, 55 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bergh et al (U.S. Pat. 4,925,796) in view of Prieels et al (J. Biol. Chem. 256(20):10456-10463 (1981)) and Schachter et al (Methods Enzymol. 28:285-287 (1972)), as applied to claims 21-23, 25, 52, 54 and 56 above, and in further view of Demain et al (U.S. Pat. 4,178,210).

As discussed above, when taken in light of Schachter, Bergh renders obvious the compositions recited in claims 21-23, 25, 52, 54 and 56. Neither Bergh nor Schachter discloses the presence of pyruvate kinase in their compositions as recited in claim 24. However, in view of the fact that Schachter's process requires ATP, the artisan of ordinary skill would have considered the use of the well-known PEP/pyruvate kinase ATP regeneration system an obvious method of regenerating the ATP required for the ultimate synthesis of the GDP-fucose required in Bergh's fucosylation process. See, e.g., Demain at column 4, lines 23-26 ("[t]he preferred phosphate donor is phosphoenolpyruvate and its corresponding phosphotransferase enzyme, pyruvate kinase.") Thus, the claimed use of pyruvate kinase in an enzymatic system known to require ATP must be considered obvious.

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Claims 21-26, 28, 29 and 52-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bergh et al (U.S. Pat. 4,925,796) in view of Prieels et al (J. Biol. Chem. 256(20):10456-10463 (1981)) and Schachter et al (Methods Enzymol. 28:285-287 (1972)) and Demain et al (U.S. Pat. 4,178,210), as applied to claims 21-25, 52, and 54, 55 and 57, above, and in further view of Yamamoto et al (Agric. Biol. Chem. 48(3):823-824 (1984)).

As discussed above, when taken in light of Schachter and Demain, Bergh renders obvious the process recited in claims 21-25, 52, and 54, 55 and 57. None of Schachter, Demain or Bergh discloses the presence of an NADPH regenerating system as recited in claim 26, or the *in situ* generation of GDP mannose via the components recited in claims 28, 29 and 56. However, Yamamoto clearly discloses that compositions comprising the claimed ingredients, including the NADPH regenerating system (right column, page 283, lines 18-21), result in the production of GDP-fucose from GDP-mannose. Moreover, Yamamoto discloses that the GDP-fucose so synthesized is suitable for use as a fucosyltransferase substrate. See first sentence page 285. Thus, the artisan of ordinary skill, recognizing that the GDP-fucose required in Bergh's process was suitably prepared using either Yamamoto's or Bergh's system, would have been motivated

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to have included the enzymes required for said syntheses in Bergh's fucosylation compositions. Moreover, the inclusion of a pyruvate kinase/PEP system in such a composition would have been obvious in view of the requirement for GTP in the synthesis of the GDP-mannose used by Yamamoto's system.

In sum, the claims recite an assembly of the enzymes known in the prior art to be useful in the synthesis of fucosylated oligosaccharides. The artisan of ordinary skill, recognizing solely from the prior art that the claimed combinations of enzymes were suitable in the preparation of fucosylated oligosaccharides, clearly would have been motivated to have assembled the claimed ingredients into a single composition. Absent some demonstration of an unexpected result coming from the claimed combination, a holding of obviousness is clearly required.

Response to Arguments

All of applicant's argument has been fully considered but is not persuasive of error. With respect to the broadest claims, it is again respectfully submitted that applicant has done nothing more than combine the components required to generate the known starting material. With respect to the claims reciting the use of enzymes known to be required for the

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production of precursors to the GDP-fucose starting material, it is again respectfully submitted that these claims recite the assembly of elements which, based in the prior art, would have been expected to have yielded the GDP-fucose starting material. Thus, because the artisan of ordinary skill knew that the claimed elements would have been desirably combined to have yielded a desirable product, the artisan of ordinary skill would have been motivated to have combined the claimed elements.

Applicant urges that the argument in the previous office action, that the presence of a fucosyltransferase in milk does not demonstrate that one of ordinary skill would have expected the various claimed enzyme combinations to have worked together *in vitro*, is flawed. Rather, urges applicant, there would have been no expectation that the various enzyme combinations would have successfully worked together. See response of September 6, 2005, pages 6-9 and 10-13.

However, it is respectfully submitted that this analysis is not borne out by the facts. The cited prior art demonstrates that the various enzymes recited in the claims all have activity at common pH and temperature ranges, and would therefore have been expected to function together. While opinion evidence has been adduced to demonstrate the contrary proposition, that opinion evidence ignores the plain disclosure of the cited

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references, asking one of ordinary skill to ignore what the references disclose in favor of an opinion in conflict with what the references teach.

Specifically, as discussed in the prior office action, Prieels clearly demonstrates the purification of at least two fucosyltransferase activities from human milk. See, e.g., abstract. Moreover, as discussed above, Prieels discloses that the purified fucosyltransferases have a fairly wide pH optimum ranging from pH 6.5 to pH 8.5 (Prieels, e.g., Fig. 7, at page 10461), which encompasses the very pH used by Schachter, pH 8 (Schachter, page 285), to prepare GDP-fucose. Thus, while fucosyltransferases are present in the golgi as argued by applicant, and the golgi does in fact have a different pH, Prieels demonstrates that fucosyltransferases may also be isolated from sources other than the golgi. Prieels also demonstrates that fucosyltransferase have properties which would motivate the artisan of ordinary skill to use them in combination with the enzymes disclosed by Schachter as producing the GDP-fucose donor moiety required by the fucosyltransferases. In sum, the artisan of ordinary skill would have recognized from Schachter that the starting materials required for the Prieels/Bergh fucosyltransferase process would have been prepared using Schachter's enzymes at a pH directly compatible

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with Bergh's fucosyltransferases (as evidenced by Prieels). The artisan of ordinary would therefore have been motivated to have combined the enzymes responsible for production of the GDP-fucose starting material with the enzyme responsible for producing the oligosaccharide, so as to prepare the starting material for Bergh's synthesis, *in situ*.

As to the fact that the enzymes were not combined despite the knowledge of the enzymes for a considerable amount of time, contentions that the reference patents are old are not impressive absent a showing that the art tried and failed to solve the same problem notwithstanding its presumed knowledge of the references. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977). No such showing has been made.

As to the fact that the Demain patent (U.S. Pat. 4,178,210) requires an ATP regeneration system whereas applicant's process supposedly does not, it is again pointed out that the Schachter's process requires ATP, and Demain demonstrates that the PEP/pyruvate kinase ATP regeneration system was known in the art to generate ATP in multi-enzyme synthesis processes. Thus, one of ordinary skill would have recognized that Demain's methodology was useful in generating starting material required in Schachter's process. Moreover, applicant's argument that ATP is not required is confusing since applicant uses PEP/pyruvate

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kinase in exactly the manner disclosed in the prior art. See, e.g., specification at page 13 (Scheme 1), where PEP/pyruvate kinase is used to generate ATP. Thus, applicant's argument that the claimed process does not "require" ATP is entirely at odds with the process as actually disclosed. That is, applicant argues that ATP is not required in their process, yet simultaneously discloses a methodology which directly employs ATP.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

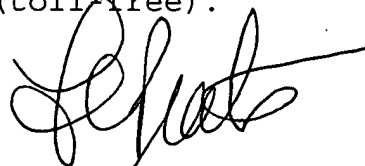
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however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Francisco C. Prats whose telephone number is 571-272-0921. The examiner can normally be reached on Monday through Friday, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Francisco C. Prats
Primary Examiner
Art Unit 1651

FCP